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SHORT COMMUNICATION

Isolation, Characterization, and Chromosomal Mapping of Mouse P450 17α-Hydroxylase/C_{17-20} Lyase

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Cytochrome P450 17α-hydroxylase/C_{17-20} lyase ($P450_{17\alpha}$) catalyzes the conversion of C-21 steroids to C-19 steroids in gonads. A full-length mouse cDNA encoding $P450_{17\alpha}$ was isolated from a mouse Leydig cell library and characterized by restriction mapping and sequencing. The predicted amino acid sequence has 83% homology to rat, 66% homology to human, and 62% homology to bovine $P450_{17\alpha}$ amino acid sequences. The protein is 507 amino acids in length, which is 1 amino acid shorter than the human protein and 2 amino acids shorter than the bovine protein. The structural gene encoding $P450_{17\alpha}$ (*Cyp17*) was localized utilizing an interspecific testcross to mouse chromosome 19, distal to *Got-1*. Another cytochrome P450, P4502c (*Cyp2c*), also is located at the distal end of chromosome 19. *CYP17*, *CYP2c*, and *GOT1* have been mapped to human chromosome 10, with *CYP2C* and *GOT1* mapped to the distal region, q24.3 and q25.3, respectively. The data in the present study indicate conserved syntenic loci on mouse chromosome 19 and human chromosome 10 and predict that the structural gene encoding $P450_{17\alpha}$ will be found distal to *GOT1* on human chromosome 10.

The biosynthesis of testosterone in Leydig cells of the testis involves the action of two cytochrome P450 enzymes, cholesterol side-chain cleavage ($P450_{scc}$) and 17α-hydroxylase/C_{17-20} lyase ($P450_{17\alpha}$), (Payne, 1990). The initial and rate-limiting step in the biosynthesis of steroid hormones is catalyzed by $P450_{scc}$, an inner mitochondrial enzyme that cleaves the side chain of cholesterol to yield the C-21 steroid, pregnenolone. Synthesis of androgens from C-21 precursors requires the activities of $P450_{17\alpha}$, which is associated with the smooth endoplasmic reticulum. $P450_{17\alpha}$ is a single protein that catalyzes two distinct reactions, the hydroxylation of the C-21 steroid progesterone or pregnenolone (17α-hydroxylase activity), followed by cleavage of the two-carbon side chain (C_{17-20} lyase activity) to yield the C-19 steroid androstenedione or dehydroepiandrosterone, respectively (Fevold *et al.*, 1989). Androstenedione is the immediate precursor of testosterone. Previous studies from this laboratory demonstrated that the expression of these two P450 enzymes is differentially regulated in mouse Leydig cells (Anakwe and Payne, 1987; Payne, 1990). $P450_{scc}$ is constitutively expressed. Treatment of Leydig cell cultures with cAMP increases steady-state levels of $P450_{scc}$ mRNA and protein synthesis. In contrast, cAMP is obligatory for *de novo* synthesis of $P450_{17\alpha}$ (Hales *et al.*, 1987; Anakwe and Payne, 1987) and accumulation of $P450_{17\alpha}$ mRNA (Payne and Sha, unpublished data). We reported previously that the structural gene for $P450_{scc}$ (*Cyp11a*) is located on mouse chromosome 9, closely linked to two other genes expressing P450 enzymes, *Cyp19*, the structural gene that encodes P450 aromatase, and *Cyp1*, the gene that expresses aryl hydrocarbon hydroxylase (Youngblood *et al.*, 1989). In a subsequent study we demonstrated that quantitative differences in the amount of Leydig cell $P450_{scc}$ enzyme protein are regulated by either the structural gene *Cyp11a* or a closely linked regulatory gene (Nolan and Payne, 1990).

To further our knowledge of the genetic and hormonal regulation of $P450_{17\alpha}$ expression in Leydig cells, a mouse Leydig cell $P450_{17\alpha}$ cDNA was isolated, characterized, and used to map the chromosomal location of the structural gene encoding $P450_{17\alpha}$ (*Cyp17*).

A mouse Leydig cell λgt11 library (Bain and Payne, unpublished data) was screened with a full-length rat $P450_{17\alpha}$ cDNA obtained from Dr. Richard Fevold (Fevold *et al.*, 1989). A clone containing a 1.7-kb insert was isolated and subcloned into Bluescript for further analysis. Figure 1 shows the restriction map of the

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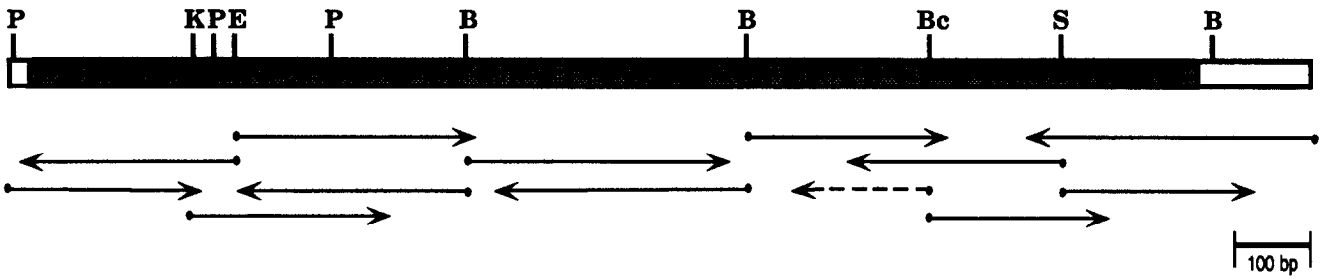

FIG. 1. Partial restriction map and sequencing strategy of mouse $P450_{17\alpha}$ cDNA. The solid bar represents the coding sequences. The open bars at each end represent the 5′ and 3′ untranslated regions. Arrows represent regions sequenced using double-stranded dideoxy sequencing of fragments cloned into Bluescript. Sequences represented by the dashed arrow were obtained using a synthetic oligonucleotide as a primer. Restriction endonuclease abbreviations: P, *Pvu*II; K, *Kpn*I; E, *Eco*RI; B, *Bam*HI; S, *Sac*I; and Bc, *Bcl*I.

mouse $P450_{17\alpha}$ and the strategy used for sequencing. The complete nucleotide sequence and the predicted amino acid sequence are given in Fig. 2. The full-length $P450_{17\alpha}$ clone contains an open reading frame of 1521 nucleotides, 32 5′ untranslated nucleotides, and 143 3′ untranslated nucleotides. A putative poly(A) addition signal is located 11 nucleotides upstream of a 17-nucleotide-long poly(A) tail. The predicted protein is 507 amino acids in length.

In Fig. 3, the complete amino acid sequence of mouse $P450_{17\alpha}$ is compared with that of rat (Fevold *et al.*, 1989), human (Chung *et al.*, 1987), and bovine (Zuber *et al.*, 1986). The mouse and rat amino acid sequences are 83% identical, while the human (66% identical) and bovine (62% identical) amino acid sequences are considerably less homologous to the mouse sequence. The mouse and rat sequences contain one less amino acid than the human and two less amino acids than the bovine. Regions of high homology common to members of the P450 gene family are shown boxed in Fig. 3. They are the putative heme binding region (aa 434–454) (Gotoh *et al.*, 1983); the Ozols tridecapeptide sequence (aa 343–372) (Ozols *et al.*, 1985), which may play a role in substrate specific-

TABLE 1

Linkage of *Cyp17* to *Emv-22* and *Got-1* on Chromosome 19 in CAST/Ei × MEV Testcross

Locus						
Emv-22[a]		*Got-1*[a]		*Cyp17*		Number
Emv-22 scored						
C[b]		C		C		28
M[b]		M		M		26
C	x[c]	M		M		9
M	x	C		C		6
C		C	x	M		2
M		M	x	C		3
C	x	M	x	C		0
M	x	C	x	M		1
					Total	75
Emv-22 not scored						
		C		C		9
		M		M		10
		C	x	M		0
		M	x	C		0
					Total	19
Emv-22	-	*Got-1*	-	*Cyp17*		
	16/75		6/94	(Recombinants/total)		
	0.213 ± 0.047		0.064 ± 0.025	(Recombination frequency ± standard error)		

[a] Segregation data for *Emv-22* and *Got-1* were reported previously (15).
[b] Alleles inherited from the CAST/Ei and MEV strains are denoted by the letters C and M, respectively.
[c] An x is used to denote regions of recombination.

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                                                                                    (32)
                                                                 ccagctggccatctgcctacacctggctgcc
                                                                                   (107)
ATG TGG GAA CTT GTG GGT CTC TTG CTG CTC ATC CTG GCC TAT TTC TTT TGG CCC AAG TCA AAG ACA CCT AAT GCC
Met Trp Glu Leu Val Gly Leu Leu Leu Leu Ile Leu Ala Tyr Phe Phe Trp Pro Lys Ser Lys Thr Pro Asn Ala
1                                                                                          (182)
AAG TTC CCC AGG AGC CTT CCA TTC CTG CCC CTG GTG GGT AGT CTA CCG TTT CTC CCC AGA CGT GGT CAT ATG CAT
Lys Phe Pro Arg Ser Leu Pro Phe Leu Pro Leu Val Gly Ser Leu Pro Phe Leu Pro Arg Arg Gly His Met His
26                                                                                         (257)
GCC AAC TTC TTC AAG CTG CAG GAA AAG TAT GGT CCC ATC TAT TCT CTT CGC CTG GGT ACC ACA ACT GCA GTG ATT
Ala Asn Phe Phe Lys Leu Gln Glu Lys Tyr Gly Pro Ile Tyr Ser Leu Arg Leu Gly Thr Thr Thr Ala Val Ile
51                                                                                         (332)
GTC GGT CAC TAT CAG CTG GCC AGA GAA GTG CTC GTG AAG AAG GGG AAA GAA TTC TCT GGT CGG CCC CAG ATG GTG
Val Gly His Tyr Gln Leu Ala Arg Glu Val Leu Val Lys Lys Gly Lys Glu Phe Ser Gly Arg Pro Gln Met Val
76                                                                                         (407)
ACT CTA GGC CTC TTG TCG GAC CAA GGA AAA GGC GTC GCC TTT GCG GAT AGT AGT AGC TCC TGG CAG CTG CAC CGG
Thr Leu Gly Leu Leu Ser Asp Gln Gly Lys Gly Val Ala Phe Ala Asp Ser Ser Ser Ser Trp Gln Leu His Arg
101                                                                                        (482)
AAG CTG GTA TTC AGC ACC TTT TCC CTG TTC AGG GAT GAC CAG AAA CTG GAG AAG ATG ATA TGT CAG GAA GCC AAC
Arg Leu Val Phe Ser Thr Phe Ser Leu Phe Arg Asp Asp Gln Lys Leu Glu Lys Met Ile Cys Gln Glu Ala Asn
126                                                                                        (557)
TCA CTG TGT GAC TTG ATA CTT ACA TAC GAC GGG GAG TCC CGA GAT CTG TCT ACG CTC ATC TTC AAG TCA GTA ATC
Ser Leu Cys Asp Leu Ile Leu Thr Tyr Asp Gly Glu Ser Arg Asp Leu Ser Thr Leu Ile Phe Lys Ser Val Ile
151                                                                                        (632)
AAT ATC ATC TGT ACC ATC TGC TTC AAC ATC TCT TTT GAG AAC AAG GAT CCG ATA CTG ACT ACC ATA CAG ACC TTT
Asn Ile Ile Cys Thr Ile Cys Phe Asn Ile Ser Phe Glu Asn Lys Asp Pro Ile Leu Thr Thr Ile Gln Thr Phe
176                                                                                        (707)
ACA GAG GGT ATT GTG GAT GTC CTG GGC CAC AGC GAT CTG GTG GAC ATA TTC CCG TGG TTG AAG ATT TTT CCC AAT
Thr Glu Gly Ile Val Asp Val Leu Gly His Ser Asp Leu Val Asp Ile Phe Pro Trp Leu Lys Ile Phe Pro Asn
201                                                                                        (782)
AAA AAC TTG GAA ATG ATA AAG GAA CAC ACT AAA ATT CGA GAA AAA ACA CTG GTT GAA ATG TTT GAA AAA TGC AAG
Lys Asn Leu Glu Met Ile Lys Glu His Thr Lys Ile Arg Glu Lys Thr Leu Val Glu Met Phe Glu Lys Cys Lys
226                                                                                        (857)
GAG AAA TTC AAT AGT GAA TCT CTC TCC AGC CTG ACA GAC ATT CTG ATA CAA GCC AAG ATG AAT GCA GAA AAT AAT
Glu Lys Phe Asn Ser Glu Ser Leu Ser Ser Leu Thr Asp Ile Leu Ile Gln Ala Lys Met Asn Ala Glu Asn Asn
251                                                                                        (932)
AAC ACT GGG GAA GGC CAG GAC CCA AGT GTG TTC TCA GAT AAG CAT ATC CTT GTC ACG GTG GGA GAC ATC TTT GGG
Asn Thr Gly Glu Gly Gln Asp Pro Ser Val Phe Ser Asp Lys His Ile Leu Val Thr Val Gly Asp Ile Phe Gly
276                                                                                       (1007)
GCA GGC ATA GAG ACA ACT AGC TCT GTG CTG AAC TGG ATC CTG GCT TTC CTG GTG CAC AAT CCT GAG GTG AAG AGG
Ala Gly Ile Glu Thr Thr Ser Ser Val Leu Asn Trp Ile Leu Ala Phe Leu Val His Asn Pro Glu Val Lys Arg
301                                                                                       (1082)
AAG ATC CAA AAG GAG ATT GAC CAG TAT GTA GGC TTC AGT CGA ACA CCG TCT TTC AAT GAC CGG ACT CAC CTC CTC
Lys Ile Gln Lys Glu Ile Asp Gln Tyr Val Gly Phe Ser Arg Thr Pro Ser Phe Asn Asp Arg Thr His Leu Leu
326                                                                                       (1157)
ATG CTG GAG GCC ACT ATC CGA GAA GTG CTT CGT ATC AGG CCG GTG GCC CCC TTG CTC ATC CCA CAC AAG GCT AAC
Met Leu Glu Ala Thr Ile Arg Glu Val Leu Arg Ile Arg Pro Val Ala Pro Leu Leu Ile Pro His Lys Ala Asn
351                                                                                       (1232)
ATT GAC TCC AGC ATT GGA GAG TTT GCC ATC CCG AAG GAC ACA CAT GTG ATC ATC AAT CTC TGG GCA CTG CAT CAC
Ile Asp Ser Ser Ile Gly Glu Phe Ala Ile Pro Lys Asp Thr His Val Ile Ile Asn Leu Trp Ala Leu His His
376                                                                                       (1307)
GAT AAA AAT GAA TGG GAC CAG CCA GAT CGG TTT ATG CCT GAG CGC TTC TTA GAT CCA ACA GGA AGC CAT CTC ATT
Asp Lys Asn Glu Trp Asp Gln Pro Asp Arg Phe Met Pro Glu Arg Phe Leu Asp Pro Thr Gly Ser His Leu Ile
401                                                                                       (1382)
ACA CCC ACA CCC AGT TAT TTA CCC TTC GGA GCT GGT CCC CGA TCG TGC ATT GGA GAG GCT CTG GCC CGG CAG GAG
Thr Pro Thr Pro Ser Tyr Leu Pro Phe Gly Ala Gly Pro Arg Ser Cys Ile Gly Glu Ala Leu Ala Arg Gln Glu
426                                                                                       (1457)
CTC TTT ATC TTC ATG GCC TTG CTG CTG CAG AGG TTT GAC TTT GAT GTG TCA GAT GAC AAA CAG CTG CCC TGT CTG
Leu Phe Ile Phe Met Ala Leu Leu Leu Gln Arg Phe Asp Phe Asp Val Ser Asp Asp Lys Gln Leu Pro Cys Leu
451                                                                                       (1532)
GTG GGT GAC CCC AAG GTG GTC TTT CTG ATC GAC CCT TTC AAA GTG AAA ATC ACA GTG CGA CAA GCA TGG AAG GAT
Val Gly Asp Pro Lys Val Val Phe Leu Ile Asp Pro Phe Lys Val Lys Ile Thr Val Arg Gln Ala Trp Lys Asp
476                                                                                       (1631)
GCA CAG GTT GAG GTT AGC ACC TAG aggccgaatctaacgtccggatcccatgccttgacacccacagcccaatcttagaggtgcctccaacaatcctcc
Ala Gln Val Glu Val Ser Thr End
501
                                                                   (1715)
tcactcctatcccgttttctacttggcagcaatgaagggtgaagacacatattaaaggttttccaataaaaaaaaaaaaaaaa
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FIG. 2. Nucleotide and predicted amino acid sequence of mouse $P450_{17\alpha}$. The putative poly(A) addition signal is underlined. Numbers on the left and under the line indicate the amino acid position. Numbers on the right, above the line and in parentheses, indicate the nucleotide position.

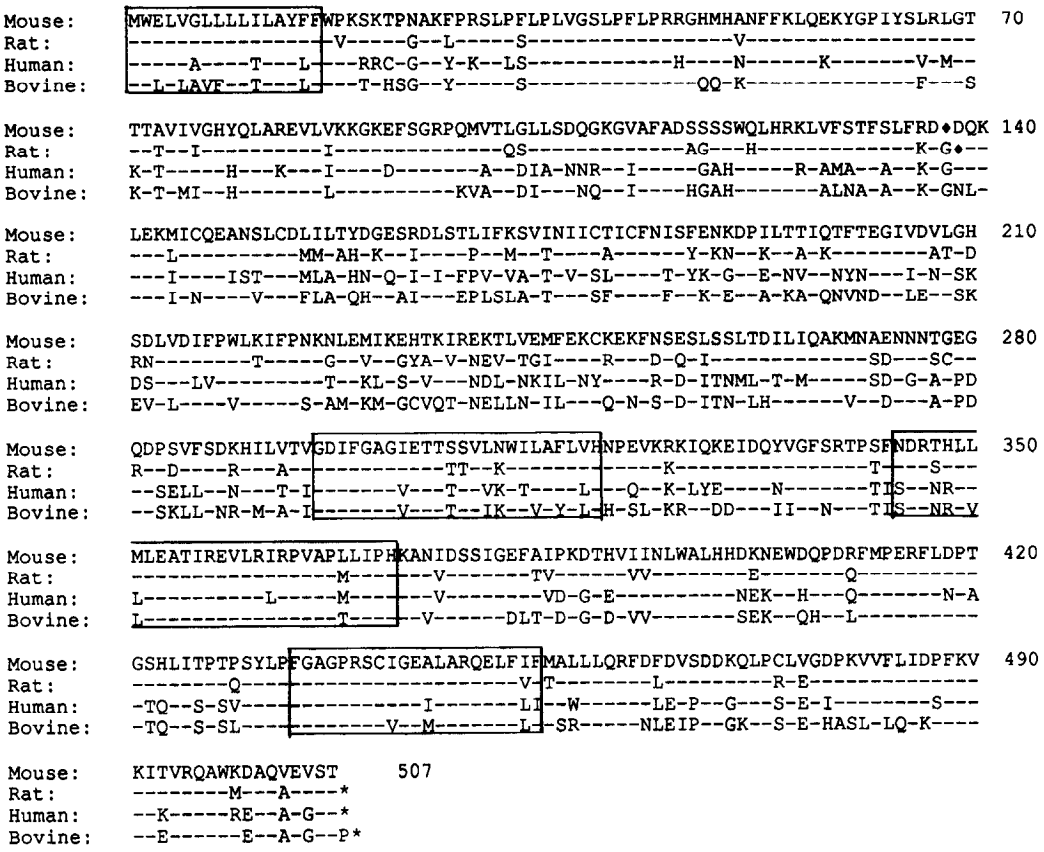

FIG. 3. Comparison of the predicted amino acid sequences of mouse, rat, human, and bovine $P450_{17\alpha}$. Boxed regions indicate conserved sequences common to members of the P450 gene family: the N-terminal hydrophobic region, the unique $P450_{17\alpha}$ sequence (amino acids 296–319); the Ozols tridecapeptide region (343–372), and the heme binding region (434–454). Diamonds (♦) indicate sites where comparable amino acids are absent. Dashes (—) indicate identity.

ity (Zuber *et al.*, 1986); and a region specifically conserved among different species of $P450_{17\alpha}$ (aa 296–319), which may function in catalysis (Ono *et al.*, 1988). The functions of other highly conserved regions seen in Fig. 3 are unknown at present.

To map *Cyp17* initially, genomic DNA from A/J and C57BL/6J, the progenitor strains for 43 recombinant inbred strains of mice, was examined for a restriction fragment length variant (RFLV) between the two progenitor strains. An unambiguous RFLV could not be identified after digestion with 19 restriction enzymes and analysis by Southern blotting. Therefore, the DNA from the intersubspecific testcross recently described by Taylor and Rowe (1989) and Warden *et al.* (1989) was examined. This testcross involved mating the CAST/Ei strain (inbred from *Mus musculus castaneus*) to the newly established MEV linkage testing stock to produce an F_1 hybrid, which was then mated to either the BXD-32 recombinant inbred strain or the SWR/J inbred strain to produce the testcross generation. The purpose of this testcross was to map several of the endogenous ecotropic murine leukemia virus proviruses present in the MEV stock, utilizing multiple biochemical and DNA variants of CAST/Ei distinguishing it from most laboratory strains. Southern blot analysis of DNA from the four progenitor strains, CAST/Ei, MEV, BXD-32, and SWR/J, identified an RFLV with the restriction enzyme *Eco*RI for the mouse $P450_{17\alpha}$ cDNA. Fragments of 7.1 and 4.6 kb were detected in CAST/Ei DNA, while 6.4- and 4.6-kb fragments were detected in MEV, BXD-32, and SWR/J DNA (Fig. 4). All three bands are present in (CAST/Ei × MEV)F_1 DNA (data not shown). Genomic DNA from 94 interspecific testcross mice was hybridized and scored for the presence or absence of the 7.1-kb *Eco*RI fragment detected in CAST/Ei. Figure 4 is a representative autoradiograph that illustrates the presence or absence of the CAST/Ei associated fragment. The distribution of alleles in the 94 testcross progeny was compared to previously mapped loci. *Cyp17* shows significant linkage with the ecotropic provirus insertion (*Emv-22*) and glutamate oxaloacetate transaminase-1 (*Got-1*) loci on chromosome 19 (Table 1). The apparent gene order and estimated recombination frequencies are *Emv-22*–0.213

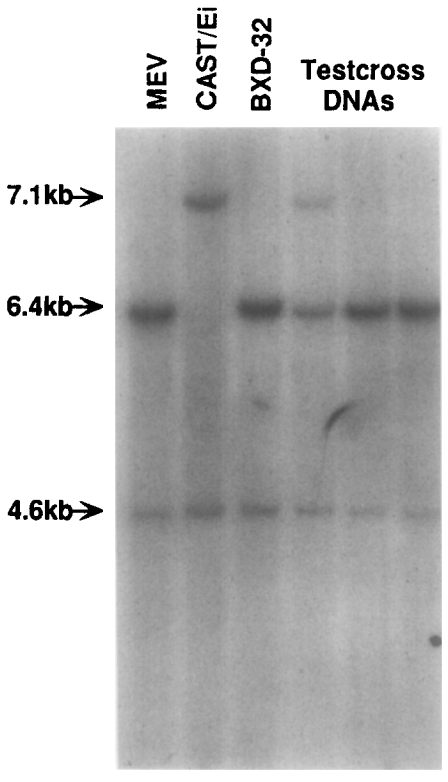

FIG. 4. Autoradiogram of a Southern blot of *Eco*RI-digested genomic DNA hybridized with the full-length mouse $P450_{17\alpha}$ cDNA. The first three lanes show the hybridized fragments of DNA from the progenitor strains indicated (SWR/J not shown). The last three lanes are representative testcross strains showing the presence or the absence of the CAST/Ei allele. Arrows indicate the length of the fragments in kilobases.

± 0.047–*Got-1*–0.064 ± 0.025–*Cyp17*. This gene order requires postulating only a single double crossover, while alternative gene orders require a minimum of five doubles. Thus, *Cyp17* maps to the distal end of chromosome 19, presumably close to esterase-18 (*Es-18*, von Deimling, 1988). Recently, another member of the P450 gene family, *Cyp2c*, associated with constitutive expression of aryl hydrocarbon hydroxylase, was mapped to the distal end of mouse chromosome 19 using Chinese hamster/mouse somatic cell hybrids and *in situ* hybridization (Meehan *et al.*, 1988a). The linkage of *Cyp2c* and *Got-1* on chromosome 19 was not determined. The human homologs of *Got-1* (Grezschik and Kazaian, 1985) and *Cyp2c* (Meehan *et al.*, 1988b) have been mapped to chromosome 10q24.3 and 10q25.3, respectively, indicating that these two genes are found in the same region of human chromosome 10, with *GOT1* mapping distal to *CYP2C*. The human gene for $P450_{17\alpha}$, *CYP17*, has also been mapped to human chromosome 10 (Matteson *et al.*, 1986) but the region of chromosome 10 was not identified. The localization of *Cyp17* 6.4 cM distal of *Got-1* on mouse chromosome 19 predicts that *CYP17* will be found in the homologous region of human chromosome 10 close to *GOT1*.

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